REMARKS

Applicant respectfully requests reconsideration and allowance of claims 1, 3, 4 and 10-13 that are pending in the above-identified patent application. Applicant has canceled claim 2, amended claims 1, 3 and 4 and added new claims 10-13. No new matter has been added by the claim amendments. Support for new claims 10-13 is found for example on page 16 of the specification as filed.

The Office Action and Notice to Comply states that the Sequence Listing as originally filed fails to comply with 37 CFR 1.821(a)(1) and (2) because sequence disclosures appear on pages 4 and 7 of the specification as filed but are not listed in the Sequence Listing . In response, Applicant has requested that the Examiner enter the attached substitute sheets containing a substitute Sequence Listing, which includes the sequences listed on pages 4 and 7 of the specification and identified as SEQ ID NO. 26, SEQ ID NO. 27 and SEQ ID NO. 28. The Applicant has also amended the header information to properly identify the continuity data for the application. The substitute Sequence Listing is supported by the application as original filed and does not include any new matter. Also included herewith are two diskettes, each containing the substitute Sequence Listing in computer readable form (CRF).

Pursuant to 37 C.F.R. § 1.821(f), the undersigned states that the substitute Sequence Listing content of the paper copy and the computer readable form (CRF) contained on the diskettes are identical.

In view of the foregoing submissions and amendments to the instant application, Applicant submits that the requirements under 37 C.F.R. §§ 1.821-1.825 have been met and the Notice to Comply has been completely addressed.

The specification is also amended as set forth hereinabove indicating the respective SEQ ID NOs. following each sequence.

In the Office Action at paragraph 5 the Examiner states that the provisional application (60/257,657) on which priority of the current application is based fails to provide adequate support for claims 1-4 of the application. The Applicant respectfully disagrees. The application is entitled to the priority date of the provisional apatent application because the provisional application clearly states that the Applicant had realized that the mutation at position 2042 from a glycine to a cysteine/arginine was of importance for the efficiency of transduction of the replicon molecule (see page 18, lines 1-5). Unfortunately, an inadvertent calculation error occurred at that time which resulted in the Applicant stating that the mutation occurred at amino acid position 2043 rather than 2042. Note that the numbering of the amino acids follows the convention established by Lohman et al. 1999 (Science 285: 110-113) which indicates a G at position 2042. The replicons of the present invention start at amino acids 810 (the first amino acid of NS2) such that position 1233 in the sequence listings should have been complemented by 809 residues to give the 2042 designation (1233 + 809 = 2042) rather than erroneous 2043 designation (1233 + 810 = 2043). It is evident from looking at the sequence listings included in the provisional application that the mutation occurred at amino acid 1233 as listed (since the sequences as listed start at position 1 which is amino acid 810 of the NS2 domain). SEQ ID NO. 1 shows a **G** at position 1233, whereas SEQ ID NO. 3, 5 and 7 show a **C** at position 1233, and SEQ ID No. 9 shows an **R** at position 1233. Withdrawal of the comments regarding lack of priority based on 60/257,657 is therefore requested.

In the Office Action on page 3, paragraph 7 claim 1 stands rejected under 35 USC §101 as being drawn to non-statutory subject matter. The foregoing amendment to claim 1 renders moot the §101 rejection in that amended claim 1 now recites "An isolated eukaryotic cell...". Applicant respectfully requests withdrawal of this rejection.

In the Office Action on page 3, paragraphs 8-10 the Examiner rejected claims 1-4 under 35 USC §112, second paragraph as being indefinite for failing to define the structural characteristics of the HCV self-replicating polynucleotide. Claim 1 as amended now recites "a

HCV polynucleotide coding region as defined in SEQ ID NO. 1", rendering this rejection and the rejection of dependent claim 3 and 4 moot. Withdrawal of this rejection is respectfully requested.

In the Office Action on page 4, paragraphs 11-15, claims 1-4 stand rejected under 35 USC §112, first paragraph "for reasons set forth in the objection to the specification". Applicant notes there is no objection to the specification in the Office Action. The Examiner asserts the specification does not provide a reproducible method to make the isolated host cell comprising the particular self-replicating HCV polynucleotide or point to any direction to obtain such host cell, hence it would require undue experimentation to enable the invention. The Examiner requests that a deposit of the particular host cell be made to meet the enablement requirement.

Applicant observes that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). The Examiner's assertion that the specification does not provide a reproducible method to make the isolated host cell comprising the particular self-replicating HCV polynucleotide or point to any direction to obtain such host cell fails to meet the burden of establishing a reasonable basis, since as is discussed hereinbelow, the specification contains the teaching of the manner and process of making and using the invention in terms which correspond in scope to the subject matter sought to be patented. Accordingly, the specification must be taken as being in compliance with 35 U.S.C. § 112, first paragraph, "unless there is a reason to doubt the objective truth of the description that is relied upon for enabling support." (See M.P.E.P. 2164).

The Examiner is incorrect in the observation that the viruses specifically recited are required to practice the invention. Applicant respectfully reminds the Examiner that there is no question of virus here. The host cell is transfected with the DNA sequence (which, granted,

originated from a HCV virus but is isolated therefrom) and the host cell never produces a virus. The original RNA sequence from which these mutated sequences were obtained are obtainable from a publicly available source (see Lohman et al. 1999), and therefore, the original virus from which these sequences were isolated does not come into play at all during the experiments performed to isolate the polynucleotides of the invention.

Moreover, the claims meet the enablement requirement because one skilled in the art could make and use the invention without undue experimentation. Claim 1 as amended recites in pertinent part a HCV polynucleotide coding region as defined in SEQ ID NO. 1 encoding an HCV polyprotein comprising: NS2, NS3, NS4A, NS4B, NS5A, and NS5B proteins, said polynucleotide coding region further encoding an amino acid substitution at position 1233 of SEQ ID NO. 1, said substitution selected from the group consisting of: commonly designated G(2042)C and G(2042)R. Any person skilled in the art could start from the same starting point as Applicant (HCV replicon clones are publicly available from the NIH AIDS Research and reference reagents program; see www.aidsreagent.org), induce point mutation in the DNA (a technique well known in the art e.g. Ausubel et al., **1994**, Current Protocols in Molecular Biology, Wiley, New York), transfect the mutated DNA into a eukaryotic cell employing well known laboratory procedures, and reproduce the instant invention without undue experimentation. The techniques required to practice the invention are well known in the art. The specification need not include, and preferably omits, what is well known in the art. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The Applicant submits the claims as amended meet the enablement requirement of 35 USC §112, and it is not necessary for the Applicant to deposit biological material to meet this requirement. Biological material need not be deposited if it is known and readily available to the public or can be made or isolated without undue experimentation. 37 CFR 1.802(b); MPEP 2404.02; *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); *Ex Parte Hata*, 6 USPQ2d 1652 (Bd. Pat. App. & Int. 1987).

Applicant requests this rejection be withdrawn.

In the Office Action on pages 5-6, paragraphs 16-23 the Examiner rejected claims 1-4 under 35 USC §112, first paragraph as failing to comply with the written description requirement. The Examiner states that the application as filed does not reasonably convey that the Applicant reasonably had possession of the claimed invention. Namely, the Examiner asserts the application does not have possession of an isolated host cell comprising a self-replicating HCV polynucleotide comprising only one mutation of G(2042)C or any other claimed mutations rather than the mutations occurring in SEQ ID NOs 1, 2, 4, 5, 6, 7. The Applicant traverses this rejection.

Satisfaction of the written description requirement is measured by the understanding of the ordinarily skilled artisan. *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). The patent specification must describe the invention in sufficient detail that one skilled in the art can clearly conclude the inventor invented what is claimed. *Cordis Corp. v. Medtronic Ave, Inc.*, 339 F.3d 1352 (Fed. Cir. 2003). However, the disclosure as filed need not provide word for word support for the claimed subject matter at issue. *Id.*, *citing, Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). Here, the claims as amended are clearly supported by the specification as filed and the precise descriptions of the claimed subject matter ensure one skilled in the art could only conclude the inventor was in possession of the claimed subject matter.

Claim 1 as amended recites in pertinent part a HCV polynucleotide coding region as defined in SEQ ID NO. 1 encoding an HCV polyprotein comprising: NS2, NS3, NS4A, NS4B, NS5A, and NS5B proteins, said polynucleotide coding region further encoding an amino acid substitution at position 1233 of SEQ ID NO. 1, said substitution selected from the group consisting of: commonly designated G(2042)C and G(2042)R. The claim is to a clearly delineated structure, support for which is found in the specification and the sequence listings. The skilled artisan can envision the detailed chemical structure of the claimed invention. The

original SEQ ID NO.1 has been publicly available since 1999 in the Genbank database with accession number AJ238799. Here the specification teaches in detail one skilled in the art how to make and use the invention and as such conclusively proves the Applicant was in possession of the claimed invention.

As further support the Applicant was clearly in possession of the claimed subject matter at the time of filing is the recitation at page 18, line 4-5 of the application as filed, where the Applicant states: *"Also noteworthy is that, in addition to G->A at nucleotide 1, there is also an adapted mutation G->C/R at amino acid 2042 (shown as amino acid 1233 in the sequence listing since a.a. 810 of NS2 is numbered as a.a. 1 in SEQ ID) that can be found in all clones analyzed."* Moreover, this statement clearly indicates that the Applicant had realized the importance of this particular mutation.

Based on the foregoing the rejection should be withdrawn.

In the Office Action on pages7-8, paragraphs 24-29, the rejected claims 1-4 on the basis of 35 USC §112, first paragraph because the specification does not reasonably provide enablement for any other established host cell comprising HCV self-replicating polynucleotide other than ...SEQ ID NO: 2,4, 5, 6, or 7.

Applicant respectfully traverses this rejection. As set forth in detail hereinabove, Claim 1 as amended states that the polynucleotide used is based on the original SEQ ID NO.1 and further comprises a mutation at amino acid position 2042. The original SEQ ID NO.1 has been publicly available since 1999 in Genbank database with accession number AJ238799. The Applicant reiterates and incorporates the arguments made hereinabove with respect to the claims as amended meeting the enablement requirement of 35 USC §112, first paragraph. The Applicant requests this rejection be withdrawn.

With respect to the comments of the Examiner in paragraphs 27-28 of the Office Action, the Applicant observes transfected Huh-7 cells are not *transformed* and the isolated replicon-containing host cells are viable and not affected by the replication. Applicant submits the comments in paragraphs 27-28 are moot in view of the amendment to claim 1.

In view of the foregoing, Applicant submits that the instant claims are in condition for allowance. Early and favorable action is earnestly solicited. In the event there are any fees due and owing in connection with this matter, please charge same to our Deposit Account No. 11-0223.

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Respectfully submitted,

By _____

Timothy X. Gibson
Reg. No. 40,618
KAPLAN GILMAN GIBSON & DERNIER, LLP
900 Route 9 North
Woodbridge, New Jersey 07095
(732) 634-7634
Attorneys for Applicant

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